

## **The protective effect of exercise on diabetic nephropathy: the role of histidine-containing dipeptides**

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Diabetic nephropathy, a microvascular complication of diabetes mellitus, is the main cause of end stage renal failure in the Western world. In humans, the susceptibility towards diabetic nephropathy is associated with a high activity of the serum carnosinase-1 enzyme (hCN1), which is genetically determined. This hCN1 enzyme hydrolyzes circulating histidine-containing dipeptides such as carnosine and anserine. Exogenous carnosine is protective towards the development of diabetic nephropathy in rodents, lacking the active hCN1 enzyme. Physical exercise is thought to enhance endogenous circulating histidine-containing dipeptides through an active release from contracting skeletal muscle (which contain the vast majority of carnosine storage). Therefore we hypothesize that the development of diabetic nephropathy will be attenuated by exercise, especially when hCN1 activity is low.

We divided 38 non-transgenic (hCN1<sup>-</sup>) BTBR ob/ob mice and 35 transgenic (hCN1<sup>+</sup>) BTBR ob/ob mice in two groups: rest and exercise. Exercise groups were subjected to a 20-week exercise intervention (running at 10 m/min, 5 days per week) to investigate the protective effect of exercise against diabetic nephropathy and the possible involvement of endogenous histidine-containing dipeptides.

Transgenic mice show a faster deterioration of lipid metabolism and a significantly greater glomerular hypertrophy (+17.7%,  $p < 0.001$ ) compared to the mice lacking hCN1. Glomerular damage is correlated with lower levels of carnosine (Pearson  $r = 0.604$ ,  $p = 0.017$ ) and anserine (Pearson  $r = 0.850$ ,  $p < 0.001$ ) in the kidney.

Low hCN1 activity rather than exercise tends to evoke protective effects against diabetic nephropathy. This study is the first to confirm the renoprotective effect of renal histidine-containing dipeptides on a histological level.